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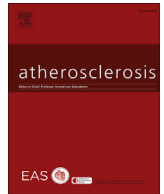
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## EAS Updates

## HEART UK statement on the management of homozygous familial hypercholesterolaemia in the United Kingdom



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## ABSTRACT

This consensus statement addresses the current three main modalities of treatment of homozygous familial hypercholesterolaemia (HoFH): pharmacotherapy, lipoprotein (Lp) apheresis and liver transplantation. HoFH may cause very premature atheromatous arterial disease and death, despite treatment with Lp apheresis combined with statin, ezetimibe and bile acid sequestrants. Two new classes of drug, effective in lowering cholesterol in HoFH, are now licensed in the United Kingdom. Lomitapide is restricted to use in HoFH but, may cause fatty liver and is very expensive. PCSK9 inhibitors are quite effective in receptor defective HoFH, are safe and are less expensive. Lower treatment targets for lipid lowering in HoFH, in line with those for the general FH population, have been proposed to improve cardiovascular outcomes. HEART UK presents a strategy combining Lp apheresis with pharmacological treatment to achieve these targets in the United Kingdom (UK). Improved provision of Lp apheresis by use of existing infrastructure for extracorporeal treatments such as renal dialysis is promoted. The clinical management of adults and children with HoFH including advice on pregnancy and contraception are addressed. A premise of the HEART UK strategy is that the risk of early use of drug treatments beyond their licensed age restriction may be balanced against risks of liver transplantation or ineffective treatment in severely affected patients. This may be of interest beyond the UK.

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## 1. Aim

This is a consensus statement by HEART UK (Hyperlipidaemia Education and Atherosclerosis Research Trust United Kingdom) on a strategy for managing homozygous familial hypercholesterolaemia (HoFH) in the UK and treating to the lower lipid targets suggested by the European Atherosclerosis Society (EAS) (Table 1) [1], which are the same as those applying to heterozygous familial hypercholesterolaemia (HeFH). It aims to provide consensus advice on the use of the three main modalities of treatment: pharmacotherapy, lipoprotein (Lp) apheresis and liver transplantation. Better treatment from birth [2] has the potential to greatly improve life expectancy in this condition. This is not intended as a didactic statement but aims to provoke discussion, form opinion and inform commissioners of healthcare and clinicians. This may be of interest outside the UK, particularly as the availability in Europe of lomitapide (see below), a proven effective but expensive cholesterol lowering therapy pharmacotherapy for HoFH, is under question [3].

## 2. Background

Familial hypercholesterolaemia (FH) is an inherited cause of very high serum cholesterol, present from birth, due to mutations affecting low density lipoprotein receptor (LDLR) activity. The prevalence of HoFH in the UK, based on the prevalence of heterozygotes of 1 in 500, is 1 in a million. Family grouping and consanguinity may result in local increases in prevalence. Some countries appear to have a higher prevalence [4,5] but diagnostic criteria vary. Prevalence in the UK and elsewhere may be underestimated because of hitherto unsuspected phenotypic variation [6]. The presence of two mutant alleles in HoFH typically raises blood cholesterol level to 4 times the age and gender related mean. Lack of LDLR activity in the liver reduces removal of low density lipoprotein cholesterol (LDLC) from the blood [7]. About 90% of cases are caused by mutations in *LDLR* [8,9] and the rest by mutations in genes affecting at least 3 other proteins [8]: apolipoprotein B (APOB) which is the main ligand for the LDLR, Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9), which reduces the recycling of LDL receptor and LDLR adaptor protein (LDLRAP1), which facilitates LDLR function. *PCSK9* mutations causing hypercholesterolaemia are due to gain of function, all the others cause loss of function of the gene product due to qualitative or quantitative defects [10,11]. Bi-allelic mutations of the *LDLRAP1* gene cause Autosomal Recessive Hypercholesterolaemia (ARH) in contrast to the much more common Autosomal Dominant Hypercholesterolaemia (ADH), which results from bi-allelic mutations in the other genes.

Lp apheresis physically removes LDL particles and is an established, safe and effective treatment for HoFH in the UK but access needs to be improved. Its availability worldwide is variable [12]. Established cholesterol lowering drugs act principally by up-regulating *LDLR* activity. Their effectiveness in HoFH is largely determined by residual LDLR activity [13]. Lomitapide and two PCSK9 inhibiting drugs, evolucumab and alirocumab, have recently been approved by the European Medicines Agency (EMA). Lomitapide

[14] is a small molecule inhibitor of microsomal triglyceride transfer protein. It reduces the hepatic assembly of very low density lipoprotein (VLDL) and intestinal chylomicrons and consequently reduces LDL-C production, an action independent of LDLR activity. Mipomersen [15], a second generation antisense oligonucleotide, which inhibits hepatic APOB synthesis has a similar effect but is not licensed by the EMA. Evolocumab and alirocumab are monoclonal antibody inhibitors of PCSK9 protein [16], which reduce LDLR catabolism and their effectiveness is determined by LDLR activity. HEART UK considers these PCSK9 inhibitors to be equivalent.

Options for treatment of HoFH also include liver transplantation [17,18] and have included portacaval shunting [19]. Liver transplantation for HoFH is uncommon in Europe and the UK, as discussed below, but is more common in some countries, possibly reflecting lack of alternatives or their cost. Portacaval shunting is now obsolete due to inconsistent cholesterol lowering and unwanted effects [20] and is not considered as an option in this statement.

There is a dilemma in the management of very young children in that treatment, including liver transplantation [21], has to begin early in life [22] to prevent serious and irreversible aortic and coronary arterial disease. However, clinical trial evidence of treatment in this age group is lacking. The question of whether liver transplantation in children offers better lifetime benefit than apheresis combined with pharmacotherapy remains unanswered [23]. There is good evidence of the safety of Lp apheresis in children but trials of lomitapide are restricted to adults over 18 years old and evolucumab to children over 12 years old. This consensus statement by HEART UK outlines a management strategy for HoFH combining Lp apheresis with lomitapide and PCSK9 inhibition with consideration of treatment of severely affected children and young adults. It is limited only to pharmacotherapy licensed for lowering LDL-C in HoFH. Our approach is to keep the choice of modality of treatment open and under continuous review for each patient and to support an interim strategy for clinical management of HoFH pending further trials. Priority is given to the early use of apheresis on the grounds of known efficacy and safety. Weekly rather than fortnightly apheresis is promoted as a means of more effective LDL-C lowering. A justification is given for more frequent apheresis based on the kinetics of the post-apheresis rebound. The need for greater availability of apheresis, in support of this strategy, is highlighted. A premise of the HEART UK clinical strategy for managing HoFH is that the early use of lomitapide and/or evolucumab, beyond their current licensed age restriction, in severely affected children and young adults should be balanced against the risks of liver transplantation [24].

## 3. Diagnosis of HoFH

Due to its hitherto unsuspected phenotypic variability, diagnosis of HoFH should not rely exclusively on LDL-C [25]. LDL-C, clinical evaluation, family history of CVD and genetic testing contribute to the accuracy of diagnosis. Each parent, necessarily, carries at least one allele causing FH. Diagnostic criteria for HoFH [1] are shown in Table 2. HoFH is likely if LDL-C > 11 mmol/L in children aged under 18 and > 13 mmol/L in adults before treatment. However, a recent study of 167 patients aged 1 to 75, with a genetic diagnosis of HoFH participating in therapeutic trials, showed untreated LDL-C ranging from 4.4 to 27.2 mmol/L [6]. Hypertriglyceridaemia reduces the predictive accuracy of LDL-C for HoFH. Cutaneous and tendon xanthomata developing before the age of 10, evidence of cardiovascular disease (CVD) and family history of premature CVD support the diagnosis and should raise suspicion with less severely elevated cholesterol values. Corneal arcus is suggestive in children and young adults, particularly if aged under 10. HoFH should be

**Table 1**  
Lipoprotein targets.

	LDL-C mmol/L	Non-HDL-C mmol/L
Adults >18	<2.5	<3.3
Adults with CVD	<1.8	<2.6
Children	<3.5	<4.3

Targets apply to the interval mean. For patients on Lp apheresis techniques lowering HDL-C only LDL-C should be used.

**Table 2**

Clinical and genetic diagnostic criteria for HoFH.

Presence of 2 disease causing alleles affecting introns and exons of the <i>LDLR</i> , <i>APOB</i> , <i>PCSK9</i> and <i>LDLRAP1</i> gene loci
Or
LDL-C >11.0 mmol/L in children with tendon or cutaneous xanthomata before age 10 or 13.0 mmol/L in adults with clinically obvious tendon or cutaneous xanthomata. But because of the now recognized genetic and clinical heterogeneity of HoFH, lower LDL-C does not exclude HoFH. Genetic diagnosis, supplementary to clinical assessment including cholesterol, is preferred.
Or
Qualifying cholesterol level and both parents with genetically confirmed HeFH

*LDLR*, low density lipoprotein receptor; *APOB*, apolipoprotein B; *PCSK9*, proprotein convertase subtilisin/kexin type 9; *LDLRAP1*, low density lipoprotein receptor adaptor protein 1 gene loci.

suspected in children if both parents have HeFH. The definition of HoFH in this statement includes ADH due to compound heterozygotes, double heterozygotes (digenic) and true homozygotes causing ARH. The genetic background determines LDLR activity, response to pharmacotherapy and the severity of disease. The presence of mutations affecting *APOB* and *LDLRAP1* have a more favourable prognosis than those affecting *LDLR* or *PCSK9* [8]. Receptor negative patients with ADH have the worst prognosis [26]. About three quarters of patients are receptor defective (residual LDLR activity (2–25%) and the rest are receptor negative (LDLR activity <2%) [27]. In a study of heterozygous familial hypercholesterolaemia (HeFH) in a French population [28], the contribution of known genes was *LDLR*, 91%, *APOB*, 8% and gain of function *PCSK9*, 1%. Based on these gene frequencies the expected gene composition in the HoFH population is: *LDLR* true homozygotes and compound heterozygotes combined, 90%, *LDLR* and *APOB* digenic heterozygotes, 8%, *LDLR* and *PCSK9* digenic heterozygotes, 1.0%, *APOB* homozygotes 0.7%, *PCSK9* digenic heterozygotes, 1% and *PCSK9* homozygotes 0.01%. ARH is very rare. *PCSK9* mutations therefore occur in about 1% of this population. In a Dutch population [29] reported gene frequencies were *LDLR*, 95% and *APOB*, 5% with no gain of function *PCSK9* discovered and in the UK *LDL-R*, 93%, *APOB* about 5% and gain of function *PCSK9* 1.7% [30]. Although the presence of a gain of function *PCSK9* allele, which increases *PCSK9* levels, in HoFH predicts a good response to *PCSK9* inhibitors, response in the HoFH population is mainly determined by residual receptor activity [31]. The functional status of many variants is currently unknown but receptor negative patients do not respond to *PCSK9* inhibitors [31].

Mutation analysis should be done by comprehensive DNA sequencing of introns and exons of the *LDLR*, *APOB*, *PCSK9* and *LDLRAP1* gene loci by an accredited laboratory. There are over 1900 [32,33] known allelic variants for the *LDLR* gene. Testing residual receptor activity would be very useful but is not generally available. High LDL-C in the range of HoFH with development of tendon and cutaneous xanthomata before the age of 10 years should be classed as HoFH even in absence of two known mutations. Failure to discover a mutation where there is a high clinical suspicion of HoFH may be due to mutations in novel genes, rare uncharacterised alleles of genes known to cause ADH or polygenic hypercholesterolaemia. A high LDL-C gene score, based on the number of single nucleotide polymorphisms (SNP) known to be associated with hypercholesterolaemia, suggests a polygenic rather than a monogenic cause [30,34]. Xanthomata also occur in sitosterolaemia [35], which has a similar clinical presentation [36] and lysosomal acid lipase deficiency [37,38], although this has distinguishing features.

#### 4. Statement 1: diagnosis of HoFH

- Patients with suspected HoFH should undergo genetic testing as this is useful for risk stratification and in the case of receptor negative patients predicts lack of response to drug treatment.

- Full informed consent should be obtained, which should include counselling on the possibility of a negative test or variation of unknown significance.
- Mutation analysis should be by comprehensive DNA sequencing of introns and exons of the *LDLR*, *APOB*, *PCSK9* and *LDLRAP1* gene loci in an accredited laboratory.
- A clinical diagnosis of HoFH should not be rejected if no mutation is found and sitosterolaemia has been excluded.
- Where no mutation is found a high LDL-C gene score supports a polygenic rather than monogenic aetiology.
- Fasting samples should be used at diagnosis to assess triglyceride levels and permit calculation of LDL-C. Indicative LDL-C levels are >11.0 mmol/L in children (aged under 18) and >13 mmol/L in adults. Lower levels should not be discounted if clinical suspicion is high.
- HoFH should be suspected if both parents have HeFH where the risk is 1 in 4.
- Once a diagnosis of HoFH is confirmed, siblings should be screened as each has a 1 in 4 chance of having the condition and a 1 in 2 chance of having HeFH.

#### 5. Clinical management of HoFH

In HoFH, very premature life threatening asymptomatic coronary arterial disease develops. Atheroma of the aortic root associated with aortic valve fibrosis, which may threaten the coronary ostia [39], may develop before the age of 5 (see management of children below). Referral to a cardiologist, for initial assessment, is recommended because of the rapidly evolving technology for non-invasive assessment of coronary arterial disease [40]. It should be explained to patients that there are limitations to non-invasive techniques and that angiography may be required for full assessment.

Cardiovascular risk factors, other than as described in this statement for lipids and aspirin, use, should be managed in accordance with UK National Guidelines. The overall benefit versus harm of aspirin use in the general population is not proven for primary prevention of cardiovascular disease but is supported by meta-analysis for secondary prevention from the age of 16 years [41]. In patients with HoFH over 16 years old, who have not had a cardiovascular event, net benefit of aspirin is a reasonable assumption because atheromatous disease is inevitable. Separate recommendations are made for children younger than 16 years old (see below) because of fewer years of exposure to high cholesterol and the heterogeneity of the condition.

#### 6. Statement 2: clinical management of adults (>18) with HoFH

- All patients should be referred to a cardiologist at diagnosis.
- Coronary and carotid arterial disease should be assessed at diagnosis with full investigation as appropriate.



- c. The gradient across the aortic valve and root should be evaluated by echocardiography at presentation and annually.
- d. There should be a clinical assessment for cardiovascular disease every 6 months and immediate investigation if cardiovascular symptoms develop.
- e. New onset or worsening angina or its equivalents such as breathlessness, easy fatigue, tachyarrhythmia or postural syncope, which may indicate aortic stenosis, should prompt early referral to a cardiologist.
- f. Flexible open access arrangements are needed to discuss cardiovascular symptoms and treatment problems. Patients should be encouraged to exercise and be taught to recognize “red flag” symptoms of cardiovascular disease.
- g. Patients should be counselled about the possibility of an acute coronary event and how to identify it and told to dial 999 if necessary.
- h. Cardiovascular disease, blood pressure, weight, diet, exercise, smoking and alcohol use should be assessed 6 monthly. Treatment response may need to be assessed more frequently if there is progression of cardiovascular disease.
- i. Other than lipid management and the use of aspirin addressed in this statement cardiovascular risk management should be in accordance with UK National Guidelines [42].
- j. Oral aspirin, 75mg once a day, to prevent atherothrombosis, should be considered from the age of 16 years (see section on children).
- k. Non-invasive testing for asymptomatic cardiac ischaemia should be considered every five years or for evaluation of symptoms as required. Computer tomography coronary angiography and cardiac magnetic resonance imaging are preferred, if available, to stress testing such as stress echocardiography [43].
- l. The lipid team should be involved if patients are admitted to hospital for any reason. An alert card with contact details should be issued.
- m. Patients should be under the long term supervision of a lipidologist experienced in managing HoFH.

## 7. Lipoprotein targets in HoFH

LDL-C lowering is the principal target for drug treatment of HoFH. Treatment targets for LDL-C, following an EAS consensus [1], are based on meta-analysis of efficacy and safety [44–46]. HoFH falls into the category of highest risk. Equivalent non-HDL cholesterol (non-HDL-C) targets may be calculated by the addition of 0.78 mmol/L (30 mg/dl) to LDL-C [42,47] as an allowance for cholesterol in triglyceride rich particles. LDL-C and non-HDL-C targets are shown in Table 1. There is no ideal, practical lipid measure for monitoring apheresis. APOB measurement may have advantages [48] but APOB in VLDL rebounds more quickly than APOB in LDL. Direct measurement of LDL-C is not widely available. Calculation of LDL-C involves assumptions about lipoprotein composition, which may not be correct following apheresis. HDL-C may be temporarily low following apheresis and since it is subtracted from total cholesterol to calculate both LDL-C and non-HDL-C, these will be overestimated. These considerations probably are only relevant in the first few days following apheresis. Weekly and longer post-apheresis values for LDL-C and non-HDL-C should not be affected. Pragmatically, calculated LDL-C and non-HDL-C are acceptable to monitor apheresis. Values of these different lipid measurements should occupy the same centile in normal population distributions in order to be equivalent [49]. Interconversion of LDL-C and non-HDL-C is problematic because the conversion factor increases with lower LDL-C and increasing triglyceride concentrations, reflecting

the lower proportion of LDL-C in non-HDL-C [50]. Therefore, non-HDL cholesterol should be measured but not inferred. A strategy for combining Lp apheresis with pharmacological treatment to achieve target lipid levels is illustrated in Fig. 1.

Gene association [51] and prospective studies [52] have established lipoprotein (a) (Lp(a)) as an independent cardiovascular risk factor. Lp(a) above 500 mg/L (125 nmol/L), measured using an isoform independent assay [53], is an independent CVD risk factor in HeFH and levels increase with gene dose [54]. However, there is no published evidence that Lp(a) is a risk factor in HoFH, where the effect of markedly raised LDL-C may overwhelm other factors. This view is supported by a post hoc analysis of a retrospective follow of CVD in 44 genetically characterised FH homozygotes [55], which showed that neither raised Lp(a) nor male gender increased the risk of CVD. However, Lp(a) might increase risk in homozygotes with LDL levels in the heterozygotes' range, either through the mild nature of the causal mutations or consequent on statin therapy, which lowers LDL but not Lp(a). Lp apheresis, lomitapide [56], evolocumab [57] and alirocumab [58] all lower Lp(a). However, priority should be given to LDL-C lowering to target values. Lp(a) should be measured pre-treatment by an isoform independent assay to allow further study of its significance in HoFH.

## 8. Statement 3: lipoprotein targets in HoFH

- a. LDL-C lowering is a proxy for clinical effectiveness.
- b. Target values for treatment should be the same as for HeFH (Table 1).
- c. Calculated LDL-C expressed as the interval mean (see below under Lp apheresis) should be used as the lipid lowering target for patients treated by Lp apheresis.
- d. Non-HDL cholesterol may be used but should be measured and not inferred from LDL-C. The measure may be unreliable immediately after apheresis, especially with double membrane filtration, which markedly reduces HDL-C.
- e. A “lower the better” approach is advocated to try to achieve EAS targets for LDL-C.
- f. Lp(a) is not a treatment target as priority is given to LDL-C (except as discussed above).

## 9. Lp apheresis

Lp apheresis physically removes LDL and VLDL and other atherogenic lipoprotein particles including Lp(a) [59]. It is established as a safe and effective first line treatment for HoFH in adults and children [13,60–66]. The commonest problems are related to complications of vascular access but anaemia due to iron deficiency is relatively common. A toolkit for setting up an Lp apheresis service has been produced by HEART UK [67]. A register of existing providers of Lp apheresis is kept by HEART UK [68]. Commercial systems have similar effectiveness and their technical specifications have been reviewed recently [65,66,69]. In HoFH, 1–2 plasma volumes need to be treated ideally at weekly intervals. However, due to resource constraints and its inconvenience, Lp apheresis is usually performed every two weeks in the UK. An acute 65–70% [70] reduction of LDL-C is established as the UK standard for performance of Lp apheresis but is intermittent. Treatment targets for cholesterol apply to the interval mean, which can be estimated using the modified Kroon equation [70,71]. More effective LDL-C lowering drug treatment may have the benefit of allowing less frequent apheresis. However the frequency of apheresis is an important determinant of the average LDL-C because of the kinetics of LDL-C rebound.

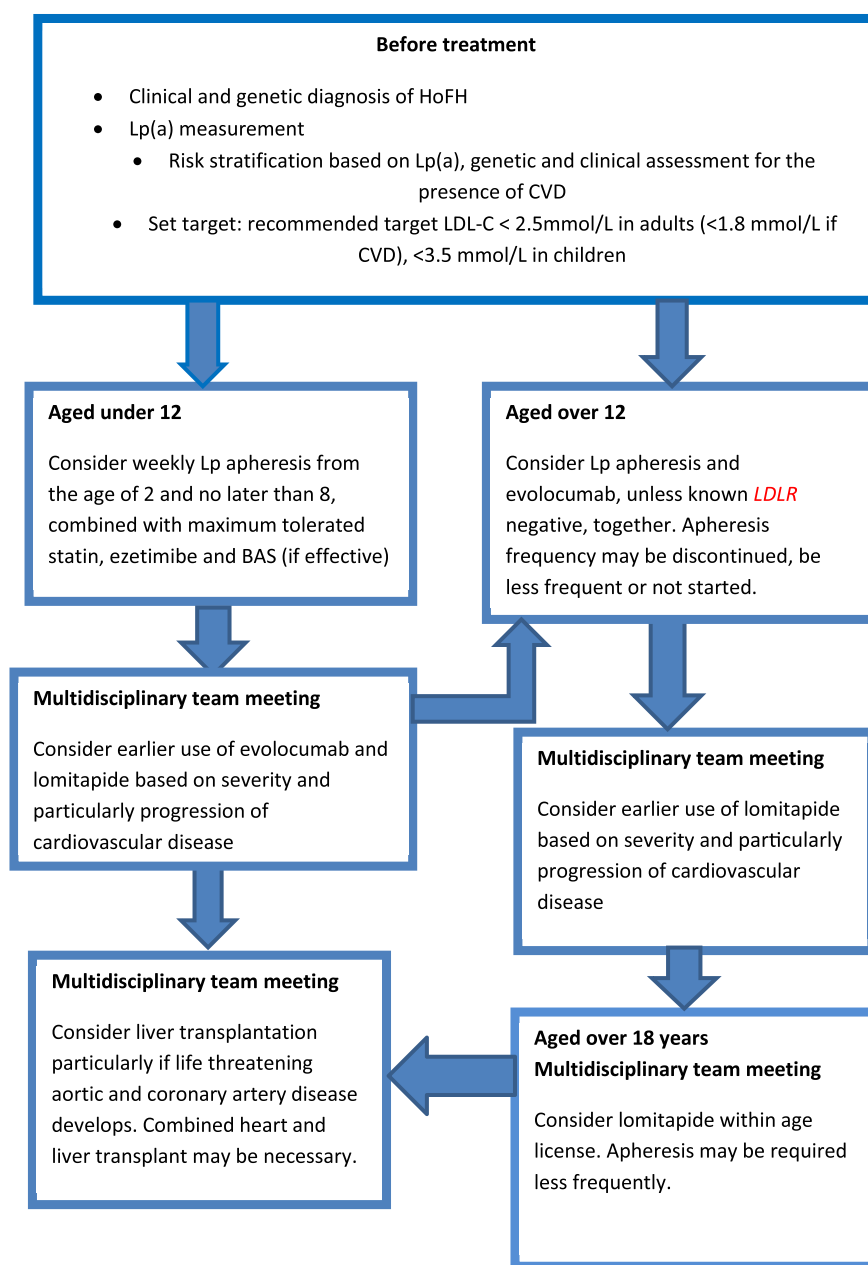


Fig. 1. Management of HoFH to new lipid treatment targets.

## 10. Kinetics of LDL-C lowering

The interval mean LDL-C calculated using the Kroon [72] equation modified [70] for HoFH as:

LDL-C interval mean =  $\alpha$  LDL-C immediately pre-apheresis + (1- $\alpha$ ) LDL-C immediately post-apheresis, where  $\alpha = 0.65$

The rebound of LDL-C following apheresis is determined by constant LDL-C production rate and a constant fractional catabolic rate (1st order kinetics). The fractional catabolic rate,  $k$ , in HoFH is about 10% per day [73]. Rebound of 50% will occur after 6.9 (0.693/ $k$ ) days, 75% at 13 (1.3/ $k$ ) days and 90% at 23 (2.3/ $k$ ) days. Provided that the LDL-C is not allowed to rebound completely 70% reduction of the pre-apheresis LDL-C will lower the post-apheresis baseline

Table 3

Predicted LDL-C interval mean from a maximum of 13.0 mmol/L, achieved by regular Lp apheresis reducing the pre-apheresis LDL-C by 70%, at different intervals.

Apheresis cycle	LDL-C rebound at 3.5 days (interval mean) mmol/L	LDL-C rebound at 7 days (interval mean) mmol/L	LDL-C rebound at 14 days (interval mean) mmol/L
1	6.6 (5.6)	8.5 (6.7)	10.8 (8.4)
2	5.3 (4.1)	7.8 (6.0)	10.6 (8.0)
3	5.0 (3.8)	7.7 (5.8)	10.6 (8.0)
4	5.0 (3.7)	7.7 (5.8)	10.6 (8.0)

See text for calculation of interval mean.

and the LDL-C will rebound to a slightly lower figure before the next apheresis. A constant value for post-apheresis is established after about 4 cycles. The shorter the interval between apheresis the greater will be the LDL-C lowering.

The rebound concentration at any time period following apheresis can be calculated as:

$$\text{LDL-C}_t = \text{LDL-C}_{\text{maximum}} - (\text{LDL-C}_{\text{maximum}} - \text{LDL-C}_{\text{immediately post-apheresis}})e^{-kt}$$

Where LDL-C is the LDL-C at time  $t$  days post-apheresis, the maximum LDL-C is the plateau concentration after apheresis when production equals removal and  $k$  is the fractional catabolic rate (about 0.1). Table 3 shows illustrative LDL-C achieved with regular apheresis at 14, 7 and between 3 and 4 days. This is the basis for our recommendation to promote weekly apheresis or even twice a week in exceptional circumstances such as pregnancy, as, because statin and other pharmacotherapy cannot be used, the rebound is more rapid [74].

Good vascular access is essential to allow efficient processing of an adequate plasma volume. However, anecdotally, among our centres in the UK, arteriovenous fistulae seem to be more problematic in Lp apheresis than in haemodialysis. The reasons remain to be defined. Vein to vein access is preferred wherever possible but early referral to create a fistula should be made if vascular access is difficult, to avoid unnecessary damage to the blood vessels. There is a need for research into improved techniques for vascular access, particularly in children.

#### 11. Statement 4: standards for an apheresis service in the UK

- The lead clinician should be an expert in lipidology and the treatment should be carried out primarily by specialist nurses.
- The unit could be embedded with other specialist units such as haematology or a dialysis unit.
- Standards should accord with those produced by HEART UK.
- Apheresis should be provided at weekly intervals unless target LDL-C concentration can be achieved with a lower frequency and adjuvant drug treatment.
- More frequent treatment, even for short periods, may be considered in exceptional circumstances such as pregnancy.
- Vein to vein access is preferred and should be used wherever possible but early referral to create a fistula should be made if access becomes difficult.
- LDL-C lowering should accord with current EAS guidelines.
- Patients should be regularly reviewed in a multi-disciplinary team meeting.
- Response to treatment and general medical issues should be discussed at least 6 monthly.
- Patients should be entered onto the UK apheresis registry run jointly by HEART UK and The Royal College of Physicians.

#### 12. Access to Lp apheresis in the UK

There are significant gaps in the provision of Lp apheresis service in the UK mainly in Scotland, Northern Ireland, the North East, East Anglia and Cornwall and Devon. New centres in these areas should be established to avoid excessive travelling. Existing services for Lp apheresis could support new centres on a hub and spoke model. NHS Blood and Transplant [75] and equivalent bodies in the devolved nations offer a range of extra-corporeal therapies and could support Lp apheresis across the UK. Commercial companies also manage an extensive network of facilities providing a range of extra corporeal treatments and could accommodate Lp

apheresis even on the small scale required for patients with HoFH. Expertise in lipidology is already sufficiently devolved to supervise treatment of HoFH provided more widely in the UK. More comprehensive coverage across the UK would encourage weekly rather than fortnightly Lp apheresis. Plasmapheresis is more widely available than Lp apheresis and may be used if Lp apheresis is not available. Lp apheresis is preferred because it is more selective.

#### 13. Statement 5: availability of Lp apheresis in the UK

- Gaps in the distribution of services should be addressed to facilitate weekly apheresis.
- There exists a wide infrastructure providing extra-corporeal therapies across the UK and these could be exploited to improve the availability of Lp apheresis.
- Lp apheresis is preferred but plasmapheresis remains an option.

#### 14. Standard drug treatment combined with apheresis for patients with HoFH

Combined treatment with rosuvastatin or atorvastatin [76] with ezetimibe [77] may lower cholesterol by up to 40% in HoFH [25,76] in patients treated by apheresis. There are no trials of BAS in HoFH but a therapeutic trial is reasonable. Survival analysis in patients with HoFH before and after the introduction of statins showed benefit measured as risk of death or time to a major adverse cardiovascular event MACE [78].

#### 15. Statement 6: standard drug treatment

- All patients should be offered maximum doses of atorvastatin or rosuvastatin combined with ezetimibe. Other statins may be tried in the event of intolerance.
- BAS may be useful in pregnancy. Colesevelam has the advantage of improved glycaemic control in type 2 diabetes [79,80] and improved tolerability.

#### 16. PCSK9 inhibitors

PCSK9 protein is increased in familial hypercholesterolaemia, being highest in HoFH, and also by HMG CoA reductase inhibitor (statin) treatment, explaining the synergy between PCSK9 inhibition and statins [81]. Evolocumab is licensed from the age of 12. Alirocumab has no license for treatment of HoFH. Evolocumab is self-administered by subcutaneous injection using a spring loaded device every 2 or 4 weeks. Phase 3 trials demonstrate safety [82,83]. Response to evolucumab in 50 HoFH patients not on apheresis depended on LDLR activity and was ineffective in its absence [31]. Responses in patients with receptor defective HoFH even with the same mutation are surprisingly variable [84] with reductions ranging from 7% to 56%, suggesting that unless patients are known to be receptor negative a therapeutic trial is worthwhile. The TAUSIG trial [85], a long term open label study of treatment of HoFH patients, with evolucumab has accumulated experience in 106 patients, including 14 adolescents, with planned 5 years of follow-up. LDL-C lowering was influenced by genotype. Mean reductions were –24% for *LDLR* defective, –6% for *LDLR* negative/negative, –51% for *PCSK9* gain of function/*LDLR* negative and –43% for ARH. Although trough levels of evolucumab were reduced following apheresis there remained full suppression of PCSK9. Evolocumab was similarly effective in patients on apheresis or not. The plasma half-life of evolucumab is between 11 and 17 days and was unaffected by apheresis in the TAUSIG study but might be

affected by more frequent apheresis. There is now considerable accumulated experience with evolucumab but there remains some concern about adverse neurocognitive effects and need for continued pharmacovigilance [86].

#### 17. Statement 7: treatment of HoFH with evolucumab

- All HoFH patients on apheresis and standard drug treatment with LDL-C above target, who are receptor defective, should have a trial of treatment with evolucumab.
- Homozygotes or compound heterozygotes with gain of function PCSK9 alleles or double heterozygotes with, for example, an *LDLR* defective allele and a gain of function PCSK9 allele (digenic) are likely to respond well to PCSK9 inhibition.
- Patients who respond with 10–15% reduction in LDL-C (or interval mean LDL-C if on Lp apheresis) should continue treatment.
- Evolucumab should be injected subcutaneously directly after apheresis.

#### 18. Lomitapide treatment for HoFH

Lomitapide is equally effective in adults with or without Lp apheresis treatment, with a mean 40%–50% [56] LDL-C reduction. However, there is considerable inter-individual variability in response [87,88] from no response to over 90% [89]. This may be partly attributed to genetic variability in the target microsomal triglyceride transfer protein [90]. The lipid lowering effects of lomitapide are not affected by Lp apheresis [91]. In phase 3 studies with extended follow up, against a background of Lp apheresis and standard drug treatment, up to 74% achieved LDL-C <2.5 mmol/L and 58% < 1.8 mmol/L [92]. This demonstrates the feasibility of achieving EAS targets in HoFH. Lomitapide is subject to a Risk Evaluation and Mitigation Strategy (REMS) [93] (Table 4) due to its predictable effects on hepatic fat accumulation, intestinal fat and fat soluble vitamin absorption. Patients should take daily supplements containing at least 400 international units of vitamin E, 200 mg of linoleic acid, 210 mg alpha-linolenic acid, 110 mg eicosapentaenoic acid and 80 mg docosahexaenoic acid. Careful dose escalation reduces the incidence of side effects, which are more common at higher doses. Account should be taken of concomitant use of cytochrome P450 3A4 inhibitors according to manufacturer's instructions. Current versions of manufacturer's instructions should be consulted. The Lomitapide Observational Worldwide Evaluation Registry (LOWER) has been established to monitor long term safety in clinical practice [94].

#### 19. Statement 8: treatment of HoFH with lomitapide

- Lomitapide should be considered for adults with HoFH, who have failed to achieve treatment targets while on apheresis and standard drug treatment and have had a trial of evolucumab.
- The frequency of Lp apheresis may be reduced when combined with lomitapide and/or evolucumab.

**Table 4**

Risk Evaluation and Mitigation Strategy (REMS) for lomitapide.

- Need for close monitoring of liver function tests and liver fat accumulation
- Restriction of use to patients accepting a low fat diet (20% of energy as fat) and restriction of alcohol use
- Fat soluble vitamin supplementation
- Baseline assessment of liver disease and regular frequent monitoring as indicated in product labelling

#### 20. Pregnancy in patients with HoFH

Pregnancy is hazardous for patients with HoFH. Lp apheresis during pregnancy is safe [95]. The risks of lipid lowering drug treatment in pregnancy are unknown. Bile acid sequestrants (BAS) with folate supplements are safe but effectiveness is uncertain. A clinical trial (NCT02399839) is addressing the effect of lomitapide exposure at conception and during pregnancy on major congenital abnormalities.

More effective treatment from an early age will make pregnancy in HoFH less hazardous. Genetic testing of the partner is desirable to exclude HeFH, especially in cultures where first cousin marriage is more common.

#### 21. Statement 9: pregnancy in patients with HoFH

- Patients should be advised that pregnancy in HoFH is hazardous.
- As a favourable outcome is uncertain, decision making should follow the principles of co-production [96] with joint decision making.
- Pre-conception, women should be referred to a cardiologist. The pressure gradient across the aortic valve and root should be assessed by echocardiography.
- Pre-conception, women with HoFH should be counselled that their children will have HeFH and if their partner has HeFH the risk of HoFH is 1 in 2.
- Women should be offered twice weekly LDL apheresis during pregnancy, if practicable, when pre-treatment LDL-C is particularly high, the LDL-C lowering during the procedure is less than desirable (target 70% acute reduction) or there is evidence of progression of cardiovascular disease.
- Careful monitoring and treatment of anaemia is essential.
- Drug treatment, other than BAS with folate supplementation should not be used as evidence of safety is lacking.

#### 22. Advice on contraception and hormone replacement treatment for patients with HoFH

Risks and benefits of contraception need to be balanced. Stopping lipid lowering drugs for an uncertain period pre-conception is particularly hazardous in HoFH. The thrombotic risk associated with hormonal contraceptive methods should be carefully assessed. Combined preparations, particularly third generation preparations should be avoided [97,98]. Up to date advice is available from The Faculty of Sexual and Reproductive Healthcare under the auspices of the Royal College of Obstetrics and Gynaecology and NICE [99]. Risks and benefits of hormone replacement treatment (HRT) should be discussed with women with postmenopausal symptoms. Parenteral preparations have the lowest thrombotic risk.

#### 23. Statement 10: advice on contraception and HRT for patients with HoFH

- Non-hormonal techniques for contraception are recommended. If essential, oral contraceptives with the lowest thrombotic risk should be selected.



- b. Survival into the menopause is uncommon at the moment but improved survival is expected. HRT is not an absolute contra-indication because post-menopausal symptoms may be severe and debilitating in some women.
- c. Risks of HRT should be discussed.
- d. HRT for relief of postmenopausal symptoms should be in the form of parenteral preparations, which have the lowest thrombotic risk.

## 24. Treatment of children with HoFH and licensing of new drugs

Atheromatous CVD develops in children with HoFH despite apheresis and conventional treatment. Aortic root atheroma is more common in children starting apheresis from the age of 10 rather than 5 and is an important cause of morbidity [100]. High priority should be given to the prevention of aortic and supra-valvular aortic disease as damage is irreversible due to fibrosis, even with subsequent effective cholesterol lowering treatment. There is, therefore, a need for early effective treatment of children [101]. The treatment volume required for Lp apheresis in children is based on weight and safety has been established over a 21 year follow up [102]. There is little or no data on the optimum means of vascular access in very young children. Atorvastatin, rosuvastatin, simvastatin, fluvastatin and ezetimibe are licensed for use in children over 10 years old. Pravastatin is licensed from the age of 8. BAS other than colesevelam are licensed from the age of age 6. The TESLA Part B study of evolucumab included patients with HoFH from the age of 12 [84]. The TAUSIG study, which included 14 adolescents, showed equivalent response compared with adults. The study is planned to extend to 5 years. Evolocumab is licensed from the age of 12 years. The HAUSER randomised controlled trial (NCT02392559) of evolucumab is recruiting children aged 10–17 with heterozygous familial hypercholesterolaemia and is designed to evaluate LDL-C lowering and safety. It is due to report in 2017. A single arm open label trial of lomitapide in children with HoFH aged 5–18 has been agreed by the EMA (EMA/PDCO/49561/2015) and is due to start in 2016.

Liver transplantation has been used in the past and there have been recent technical advances [18]. Data from the European Liver Transplant Registry indicate that 21 liver transplants were done in Europe, including the UK, between 1988 and 2009 for HoFH recipients [103]. The population of Europe in 2009 was 743 million. Assuming a prevalence of 1 in a million fewer than 3% of HoFH patients were treated in this way. However, it may be more prevalent in other places. A series of 36 cases in Iran [104], where apheresis is not widely available has recently been published and there are several recent case descriptions of successful outcome [105–107]. The genetic and clinical heterogeneity of HoFH is now recognized and should determine the clinical management. In the UK, HoFH has a low priority rating for liver transplant but there is an option of lobar transplant [108–110] from a living related donor even if the donor is a heterozygote [111]. Because of limited organ availability, operative risk and problems of lifelong immunosuppression, liver transplant combined with heart transplantation should remain a therapeutic option for severely affected children and young adults with HoFH, as a last resort [17].

Atheromatous cardiovascular disease is rare in children without HoFH and there is no evidence to support the use of aspirin to prevent atherothrombosis. However, aspirin is commonly and safely used for other thrombotic conditions [112–114]. The presence of atheromatous disease and therefore the likely benefit of aspirin cannot be assumed, as we have for adults, due to fewer years of exposure to raised cholesterol and the clinical

heterogeneity of HoFH. Aspirin should only be considered if there is evidence of atheromatous disease. Doses should be at the low end of the dose range, 1–5 mg/Kg/day [115,116], recommended for arterial thrombotic disease in children. The anti-platelet response to aspirin should be confirmed [117]. Aspirin should be discontinued in febrile children, especially with flu like symptoms and chicken pox, to minimise the small risk of Reye's syndrome.

## 25. Statement 11: the treatment of children

- a. Children should be seen in an appropriate environment. Parents should be involved and educated and genetically counselled. Family clinics are encouraged and transition to adult clinics should be planned from age of 14–16 and transfer arranged between 16 and 18 years.
- b. Treatment should be initiated by a paediatrician with expertise in the management of HoFH.
- c. Lp apheresis should be started as soon as possible but it is difficult to get children aged younger than 5 to accept the procedure. It should be considered from the age of 2 and started before the age of 7.
- d. Lp apheresis combined with statin and ezetimibe at licensed doses should be instituted as early as possible. BAS treatment may be tried but discontinued if ineffective.
- e. Evolocumab should be considered from the age of 12 if treatment targets are not achieved.
- f. Lomitapide should be considered from the age of 18 if treatment targets are not achieved.
- g. Earlier treatment should be considered if evidence of atherosclerosis is seen, particularly when threatening the coronary ostia. Coronary angiography, performed by a paediatric cardiologist with expertise in HoFH, is preferred to stress testing in severely affected children.
- h. Low dose aspirin, 1–5 mg/Kg/day up to 75 mg, should be considered if atheromatous disease is evident. Response to aspirin should be assessed and the lowest effective dose used. Aspirin should be discontinued during febrile illness.
- i. Prescription of drugs beyond licence should follow the principles of co-production, preferably in the context of a multidisciplinary team meeting. Risk may be balanced against the benefit of avoiding aortic arch surgery or the risk of liver transplantation, which might be considered as a last resort if there has been suboptimal achievement of therapeutic target lipid levels in severely affected children.
- j. Portacaval shunt as a treatment for HoFH is now obsolete.

## 26. Commissioning treatment for HoFH in the UK

HoFH is a rare disease with estimates of prevalence in Europe ranging from 1 in 75,000 (Denmark) [4], 1 in 300,000 (Netherlands) [5] and 1 in a million in the UK. Although diagnostic methods differ, these estimates show that HoFH is considerably rarer than the definition of a rare disease used in the Department of Health Strategy for Rare Diseases [118] of 1 in 2000. HeFH, untreated, is associated with premature cardiovascular disease and occurs in 1 in 500 of the UK population but is effectively treated with statins. As described above HoFH is much more severe than HeFH and statins are relatively ineffective. Effective treatment of HoFH with Lp apheresis, evolucumab and lomitapide is expensive per patient but the benefit is large with the possibility of a normal life expectancy. Because of its severity and its rarity, HEART UK supports the classification of HoFH as a rare disease within the UK strategy. There are approximately 80 cases of HoFH in the UK compared with up to 8000 cases of other rare diseases. This statement by HEART UK fulfils the requirement of the

strategy for a clearly defined care pathway in the UK including diagnosis, cascade screening and lifetime care.

The disastrously accelerated premature development of atheroma in HoFH has so far precluded randomised controlled trials of LDL-C lowering. However, a rationale for treatment of HoFH is provided by the huge body of data, including a meta-analysis of LDL-C lowering [46,119–123] and a Mendelian randomisation study [124], showing that reduction of CVD events relates to the extent of LDL-C lowering regardless of the mechanism. The best available data on the cardiovascular risk associated with HoFH on standard drug treatment and the potential benefit of further cholesterol reduction come from a trial of Mipomersen [125,126]. In a group of patients with FH including about half with HoFH, cardiovascular risk expressed as MACE/1000 patient months was 25.7 on standard treatment before mipomersen compared with 3.6 after [126]. Temporal advances in lipid lowering treatment of HoFH, including Lp apheresis, have improved survival and reduced adverse cardiovascular events [127].

The rarity of HoFH and its severity require special consideration of risk and benefit of treatment, especially for children. Commissioning of treatment for HoFH in the UK is the responsibility of NHS England and equivalent bodies in the devolved nations. Lomitapide is expensive for individual patients but there are only around 80 people in the UK with HoFH. The cost effectiveness of LDL-C lowering treatment is greatest when absolute cardiovascular risk and LDL-C are high, HoFH being an extreme case and is a function of absolute LDL-C reduction. The “number needed to treat” (NNT) [128] based on absolute CVD risk reduction is a useful comparator of cost-effectiveness [129]. Cholesterol lowering to new targets should markedly improve prognosis, particularly if started early in life. Evolocumab is licensed for lipid lowering in the general population and is consequently significantly cheaper than lomitapide. Cost effectiveness analysis of treatment of HoFH is complicated by the lack of controlled trials. However, in contradistinction from cholesterol lowering in the none-HoFH population, it is likely that every individual patient with HoFH will benefit clinically from cholesterol lowering in proportion to its degree i.e. NNT close to 1. A useful analogy would be, for example, antibiotic use where the NNT is close to 1. Very effective treatments are in the range 2–4. This concept may be applied to the effectiveness of treatment in achieving EAS targets for LDL-C [130] where the NNT to achieve <2.5 mmol/or <1.8 mmol/L are 2 and 4 respectively. Thus achievement of EAS targets can be achieved, even with monotherapy with lomitapide, in a substantial proportion of patients.

## 27. Statement 12: commissioning treatment for HoFH in the UK

- HoFH should be adopted as a rare disease within the UK strategy for rare diseases.
- Lp apheresis and treatment with lomitapide and evolocumab should be commissioned as a package to allow optimal and cost effective combination treatment.
- Estimation of treatment cost effectiveness should take into account total cardiovascular risk, the baseline LDL-C and its absolute reduction and the number needed to treat, especially when considering the incremental benefit of new treatments.
- In children, the presence of atheromatous disease in anatomically critical sites should be taken into account when judging the risks, benefits and cost of early drug treatment.

## Conflict of interest

The authors declared they do not have anything to disclose

regarding conflict of interest with respect to this manuscript.

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